UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
07/565,673	08/10/1990	JOHANNES C. VAN DER LAAN		8222

7590 04/26/2004

DEBRA J. GLAISTER PATENT AGENT
GENENCOR INTERNATIONAL INC.
925 PAGE MILL ROAD
PALO ALTO, CA 94304

EXAMINER	
FRONDA, CHRISTIAN L	
ART UNIT	**PAPER NUMBER**
1652	

DATE MAILED: 04/26/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No. 07/565,673	Applicant(s) VAN DER LAAN ET AL.	
	Examiner Christian L Fronda	Art Unit 1652	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☐ Responsive to communication(s) filed on _____.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *41-55* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *41-55* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☒ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

1. In view of the Appeal Brief filed on April 23, 2002, PROSECUTION IS HEREBY REOPENED. Previous rejections and grounds of rejections have been withdrawn in favor of new rejections and grounds for rejection as set forth below.

To avoid abandonment of the application, appellants must exercise one of the following two options:

(1) file a reply under 37 CFR 1.111 (if this Office action is non-final) or a reply under 37 CFR 1.113 (if this Office action is final); or,

(2) request reinstatement of the appeal.

If reinstatement of the appeal is requested, such request must be accompanied by a supplemental appeal brief, but no new amendments, affidavits (37 CFR 1.130, 1.131 or 1.132) or other evidence are permitted. See 37 CFR 1.193(b)(2).

2. Claims 41-55 are under consideration in this Office Action.

Claim Rejections - 35 U.S.C. § 112, 1st Paragraph

3. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

4. Claims 41-55 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Beginning on page 10 of the Appeal Brief, appellants' position is that adequate written description support is found in the specification, various Bacillus strains are stated in the specification, several Bacillus strains were known to one of general skill in the art at the time the application was filed, and it is not necessary to describe the numerous wild-type or mutant

proteases since it is asserted that the specification shows how a wild-type protease can be obtained from an alkalophilic Bacillus strain and after deletion of the wild-type protease gene one skilled in the art could transform the Bacillus with a gene encoding a heterologous protease. The Examiner respectfully disagrees with applellants' position that claims 41-55 are adequately described by the specification for the following reasons.

MPEP §2111 states that claims must be given their broadest reasonable interpretation consistent with the specification and that such interpretation of the claims must also be consistent with the interpretation that those skilled in the art would reach. The claims of the instant invention must be read in light of the specification to thereby interpret limitations explicitly recited in the claims. Thus, limitations of the specification cannot be read into the claims to narrow the scope of the claims by implicitly adding disclosed limitations which are not recited in the claims.

According to the Appeal Brief on page 8, high alkaline proteases are defined as "proteases produced by alkalophilic Bacillus strains". According to the specification "alkalophilic bacilli are defined as Bacillus strains that grow under alkaline conditions" (see p. 10, lines 23-25).

Thus, in view of MPEP §2111, page 8 of the Appeal Brief and page 10, lines 23-25, of the specification, claim 50 is deemed to be a genus claim which encompasses any mutant alkalophilic Bacillus strain which grows under alkaline conditions and produces any **mutant protease** of any amino acid sequence and structure, and has no detectable level of any **intracellular or extracellular wild-type protease** of any amino acid sequence and structure resulting from any genetic mutation to the mutant alkalophilic Bacillus strain, where the wild-type protease is encoded by a gene having any nucleotide sequence and structure.

The scope of claim 50 is highly variant and includes many intracellular or extracellular wild-type protease genes with widely differing structural, chemical, and physical characteristics which encode any wild-type protease of any amino acid sequence and structure, where any of these genes encoding any intracellular or extracellular wild-type protease is manipulated by any genetic modification such that there is no detectable activity of the wild-type protease in the claimed mutant alkalophilic Bacillus strain. The scope of claim 50 includes many mutant protease from many biological sources with widely differing structural, chemical, and physical characteristics, where the mutant protease is produced in the claimed mutant alkalophilic Bacillus strain.

One skilled in the relevant art would know that there are many classes of intracellular and extracellular proteases known at the time the application was filed and that the classes of known proteases include serine proteases, metallo proteases, cysteine proteases, threonine protease, and aspartyl proteases. Thus, the scope of proteases encompassed by claim 50 includes wild-type and mutant serine proteases, metallo proteases, cysteine proteases, threonine proteases, and aspartyl

proteases.

The specification describes an asporogenous mutant of Bacillus novo species PB92 stain that has been genetically manipulated to have chromosomal the wild-type Bacillus PB92 extracellular serine protease gene replaced with an inactive gene fragment containing only the 5' and 3'flanking sequences of the Bacillus PB92 extracellular serine protease gene, resulting in the Bacillus strain having no detectable level of Bacillus PB92 extracellular serine protease activity.

The specification describes several Bacillus strains, which have no detectable level of the wild-type Bacillus PB92 extracellular serine protease because the chromosomal wild-type gene is replaced with an inactive gene fragment containing only the 5' and 3'flanking sequences of the Bacillus PB92 extracellular serine protease gene, that are genetically manipulated either have a chromosomal replacement of the inactivated Bacillus PB92 extracellular serine protease gene with a mutant Bacillus PB92 extracellular serine protease gene that expresses a functional mutant Bacillus PB92 extracellular serine protease or are genetically manipulated to contain a plasmid containing a mutant Bacillus PB92 extracellular serine protease gene that expresses a functional mutant Bacillus PB92 extracellular serine protease.

The described mutant alkalophilic Bacillus strains, which have no detectable level of the wild-type Bacillus PB92 extracellular serine protease because the chromosomal wild-type gene is replaced with an inactive gene fragment containing only the 5' and 3'flanking sequences of the Bacillus PB92 extracellular serine protease gene and are genetically manipulated either to have a chromosomal replacement of the inactivated Bacillus PB92 extracellular serine protease gene with a mutant Bacillus PB92 extracellular serine protease gene that expresses a functional mutant Bacillus PB92 extracellular serine protease or are genetically manipulated to contain a plasmid containing a mutant Bacillus PB92 extracellular serine protease gene that expresses a functional mutant Bacillus PB92 extracellular serine protease, **is only representative** of a genus of mutant alkalophilic Bacillus strains having no detectable level of a wild-type extracellular serine protease, since the chromosomal wild-type gene encoding the extracellular serine protease has been replaced with an inactivated mutant extracellular serine protease gene, and producing a mutant extracellular serine protease where the gene encoding the mutant extracellular serine protease is integrated into the chromosome or is localized to a vector.

The described mutant alkalophilic Bacillus strains **is not representative** of the genus of mutant alkalophilic Bacillus strain encompassed by claim 50, where the scope of claim 50 includes many mutant alkalophilic Bacillus strains having no detectable activity of any wild-type serine protease, metallo protease, cysteine protease, threonine protease, or aspartyl protease and producing any mutant serine protease, metallo protease, cysteine protease, threonine protease, or aspartyl protease. The specification does not provide a written description of any other member of the genus of claim 50. Thus, Applicants have failed to sufficiently describe the claimed invention, in such full, clear, concise, and exact terms that a skilled artisan would recognize Applicants were in possession of the genus of claim 50. The limitations of claims 51-53 do not

overcome the defect of claim 50 and are rejected since claim 51-53 do not recite a mutant alkalophilic Bacillus strain having no detectable level of a wild-type extracellular serine protease, because the chromosomal wild-type gene encoding the extracellular serine protease has been replaced with an inactivated mutant extracellular serine protease gene, and producing a mutant extracellular serine protease.

In view of MPEP §2111, page 8 of the Appeal Brief and page 10, lines 23-25, of the specification, claim 41 is deemed a genus claim that encompasses a genus of methods for making any **mutant protease** of any amino acid sequence and structure by obtaining any non-reverting mutant alkalophilic Bacillus host that is incapable of producing any **intracellular or extracellular wild-type protease** of any amino acid sequence and structure, wherein the said non-reverting mutant alkalophilic Bacillus host comprises a chromosomal deletion of the gene of any nucleotide sequence and structure encoding the any **intracellular or extracellular wild-type protease** and contains any integration cassette comprising any gene of any nucleotide sequence and structure encoding any **mutant protease** of any amino acid sequence and structure; and growing said non-reverting mutant alkalophilic Bacillus host under conditions to express said mutant high alkaline protease.

The scope of claim 41 is highly variant and includes many chromosomal intracellular or extracellular wild-type protease genes that are to be deleted in the claimed Bacillus host, where the genes have widely differing structural, chemical, and physical characteristics which encode any widely differing intracellular or extracellular wild-type serine proteases, metallo proteases, cysteine proteases, threonine proteases, and aspartyl proteases.

The specification describes in Table 1 the relative amount of production of functional mutants of Bacillus PB92 extracellular serine protease in several Bacillus strains which have no detectable level of the wild-type Bacillus PB92 extracellular serine protease because the chromosomal wild-type gene is replaced with an inactive gene fragment containing only the 5' and 3'flanking sequences of the Bacillus PB92 extracellular serine protease gene, where the mutant gene encoding the mutant Bacillus PB92 extracellular serine proteases is localized on the chromosome of the Bacillus strain or on a plasmid.

The described relative amount of production of functional mutants of Bacillus PB92 extracellular serine protease in several Bacillus strains illustrated in Table 1 of the specification **is only representative** of a genus of methods for producing mutant proteases in a Bacillus host strain having a chromosomal deletion of the wild-type gene encoding the extracellular serine protease and containing any integration cassette comprising any gene encoding any mutant protease.

The described relative amount of production of functional mutants of Bacillus PB92 extracellular serine protease in several Bacillus strains illustrated in Table 1 of the specification **is not representative** of the entire genus of methods of claim 41, where the genus encompasses

methods for making mutant proteases in any Bacillus host strain having any chromosomal deletion of any gene of any nucleotide sequence and structure encoding any **intracellular or extracellular wild-type protease** resulting in the Bacillus host strain being incapable of producing the intracellular or extracellular wild-type protease. The specification does not provide a written description of any other member of the genus of claim 41.

Thus, Applicants have failed to sufficiently describe the claimed invention, in such full, clear, concise, and exact terms that a skilled artisan would recognize Applicants were in possession of the genus of claim 41. The limitations of claims 42-47 which depend on claim 41 do not overcome the defect of claim 41 and are rejected since claims 42-47 do not recite the described genus of methods for producing mutant proteases in a Bacillus host strain having a chromosomal deletion of the wild-type gene encoding the extracellular serine protease and containing any integration cassette comprising any gene encoding any mutant protease.

In view of MPEP §2111, page 8 of the Appeal Brief and page 10, lines 23-25, of the specification, claim 48 is deemed a genus claim that encompasses a genus of methods for making any non-reverting mutant alkalophilic Bacillus strain having a reduced level of any **intracellular or extracellular wild-type protease** of any amino acid sequence and structure by replacing the gene of any nucleotide sequence and structure encoding the any intracellular or extracellular wild-type protease with an inactivated mutant of the gene encoding the any intracellular or extracellular wild-type protease.

The scope of claim 48 is highly variant and includes many chromosomal intracellular or extracellular wild-type protease genes that are to be deleted in the claimed Bacillus host, where the genes have widely differing structural, chemical, and physical characteristics which encode any widely differing intracellular or extracellular wild-type serine proteases, metalloproteases, cysteine proteases, threonine proteases, and aspartyl proteases.

The described method for making mutant alkalophilic Bacillus strains, which have no detectable level of the wild-type Bacillus PB92 extracellular serine protease because the chromosomal wild-type gene is replaced with an inactive gene fragment containing only the 5' and 3'flanking sequences of the Bacillus PB92 extracellular serine protease gene, **is only representative** of a genus of methods for making a mutant alkalophilic Bacillus strains having a reduced level of a wild-type extracellular serine protease, where the wild-type gene encoding the wild-type extracellular serine protease is replaced with an inactive gene fragment containing only the 5' and 3'flanking sequences of the wild-type extracellular serine protease gene.

The described method for making mutant alkalophilic Bacillus strains, which have no detectable level of the wild-type Bacillus PB92 extracellular serine protease because the chromosomal wild-type gene is replaced with an inactive gene fragment containing only the 5' and 3'flanking sequences of the Bacillus PB92 extracellular serine protease gene **is not representative** of the genus of methods encompassed by claim 48 for making any non-reverting

mutant alkalophilic Bacillus strain having a reduced level of any intracellular or extracellular wild-type protease of any amino acid sequence and structure by replacing the gene of any nucleotide sequence and structure encoding the any intracellular or extracellular wild-type protease with an inactivated mutant of the gene encoding the any intracellular or extracellular wild-type protease. The specification does not provide a written description of any other member of the genus of claim 48.

Thus, Applicants have failed to sufficiently describe the claimed invention, in such full, clear, concise, and exact terms that a skilled artisan would recognize Applicants were in possession of the genus of claim 48. The limitations of claim 49 which depend from claim 48 does not overcome the defect of claim 48 and are rejected since claim 49 does not recite a method for making a mutant alkalophilic Bacillus strains having a reduced level of a wild-type extracellular serine protease, where the wild-type gene encoding the wild-type extracellular serine protease is replaced with an inactive gene fragment containing only the 5' and 3'flanking sequences of the wild-type extracellular serine protease gene

In view of MPEP §2111, page 8 of the Appeal Brief and page 10, lines 23-25, of the specification, claim 54 is deemed a genus claim that encompasses a genus of methods for making any **mutant protease** of any amino acid sequence and structure by obtaining any non-reverting mutant alkalophilic Bacillus host selected from Bacillus novo species PB92 and derivatives that retain the characteristics of Bacillus novo species PB92 that is incapable of producing any **intracellular or extracellular wild-type protease** of any amino acid sequence and structure, wherein the said non-reverting mutant alkalophilic Bacillus host comprises a chromosomal deletion of the gene of any nucleotide sequence and structure encoding the any **intracellular or extracellular wild-type protease** and contains any integration cassette comprising any mutant gene encoding any mutant Bacillus novo species PB92 protease; and growing said non-reverting mutant alkalophilic Bacillus host under conditions to express said mutant high alkaline protease.

The scope of claim 54 is highly variant and includes many chromosomal intracellular or extracellular wild-type protease genes that are to be deleted in the claimed Bacillus host, where the genes have widely differing structural, chemical, and physical characteristics which encode any widely differing intracellular or extracellular wild-type serine proteases, metallo proteases, cysteine proteases, threonine proteases, and aspartyl proteases.

The described relative amount of production of functional mutants of Bacillus PB92 extracellular serine protease in several Bacillus strains illustrated in Table 1 of the specification **is only representative** of a genus of methods for producing mutant proteases in a Bacillus host strain having a chromosomal deletion of the wild-type gene encoding the extracellular serine protease and containing any integration cassette comprising any gene encoding any mutant protease.

The described relative amount of production of functional mutants of Bacillus PB92

extracellular serine protease in several Bacillus strains illustrated in Table 1 of the specification **is not representative** of the entire genus of methods of claim 54, where the genus encompasses methods for making mutant proteases in the recited Bacillus host strain having any chromosomal deletion of any gene of any nucleotide sequence and structure encoding any **intracellular or extracellular wild-type protease** resulting in the Bacillus host strain being incapable of producing the intracellular or extracellular wild-type protease.

Thus, Applicants have failed to sufficiently describe the claimed invention, in such full, clear, concise, and exact terms that a skilled artisan would recognize Applicants were in possession of the genus of claim 54. The limitations of claim 55 do not overcome the defect of claim 54 and is rejected since claim 55 does not recite the described genus of methods for producing mutant proteases in a Bacillus host strain having a chromosomal deletion of the wild-type gene encoding the extracellular serine protease and containing any integration cassette comprising any gene encoding any mutant protease.

Claim Rejections - 35 U.S.C. § 102

5. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless --
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

6. Claim 48 is rejected under 35 U.S.C. 102(b) as being anticipated by Fahnestock et al. [Appl Environ Microbiol. 1987 Feb;53(2):379-84]

According to the Appeal Brief on page 8, high alkaline proteases are defined as "proteases produced by alkalophilic Bacillus strains". According to the specification "alkalophilic bacilli are defined as Bacillus strains that grow under alkaline conditions" (see p. 10, lines 23-25).

Thus, in view of MPEP §2111, page 8 of the Appeal Brief and page 10, lines 23-25, of the specification, claim 48 is deemed a genus claim that encompasses a genus of methods for making any non-reverting mutant alkalophilic Bacillus strain having a reduced level of any **intracellular or extracellular wild-type protease** of any amino acid sequence and structure by replacing the gene of any nucleotide sequence and structure encoding the any intracellular or extracellular wild-type protease with an inactivated mutant of the gene encoding the any intracellular or extracellular wild-type protease.

Fahnestock et al. teach a method for making a mutant, non-reverting protease-deficient Bacillus host strains that have insertion or deletion mutations in the subtilisin structural gene (apr) which produced no subtilisin and no detectable extracellular metalloprotease activity, both of which are the most abundant proteases produced in Bacillus species (see entire publication).

Fahnestock et al. teach the subtilisin gene (apr) was inactivated by insertion of cat gene of pC194 into the apr gene resulting in the separation of the promoter and secretion signal sequence from most of the protein-coding sequence and active-site residues (see p.380-381, and Figures 1 and 2). The resulting inactivate apr gene is deemed to be a mutant apr gene having the wild-type 5' and 3' flanking non-coding regions of the apr gene, and the region interrupted by and containing the cat gene is deemed to no longer be the coding region of the wild-type apr gene.

The inactivated apr gene was introduced by a shuttle vector into Bacillus subtilis where the inactivated apr gene was integrated into the chromosome by homologous recombination, the plasmid sequences excised in subsequent recombination event thereby eliminating any replication function of the plasmid, the Bacillus subtilis containing the inactivated apr gene were culture, and strains that have reduced extracellular serine protease and metalloprotease activities were isolated (see p. 382-383, and Tables 1 and 2).

Thus, the reference teachings anticipate the claimed method for making any non-reverting mutant alkalophilic Bacillus strain having a reduced level of any intracellular or extracellular wild-type protease of any amino acid sequence and structure by replacing the gene of any nucleotide sequence and structure encoding the any intracellular or extracellular wild-type protease with an inactivated mutant of the gene encoding the any intracellular or extracellular wild-type protease

Claim Rejections - 35 U.S.C. § 103

7. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any

evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

8. Claims 41, 42, 45-47, 50, and 52 are rejected under 35 U.S.C. 103(a) as being unpatentable over Fahnestock et al. [Appl Environ Microbiol. 1987 Feb;53(2):379-84] in view of Takagi et al. [J Biol Chem. 1988 Dec 25;263(36):19592-6].

In addition to the teachings stated above, Fahnestock et al. teach mutant, non-reverting protease-deficient Bacillus host strains and method of making protease-deficient Bacillus host strains that have insertion or deletion mutations in the subtilisin structural gene (apr) which produced no subtilisin and no detectable extracellular metalloprotease activity, both of which are the most abundant proteases produced in Bacillus species; protease-deficient Bacillus host strains containing a plasmid comprising the Staphylococcus aureus apa-1 gene encoding staphylococcal protein A were used to produce and accumulate staphylococcal protein A; and Fahnestock et al. teach that these protease-deficient Bacillus host strains are superior host strains for the production of foreign proteins since the reduced protease levels allows for the accumulation of produced foreign proteins with less degradation (see Abstract and entire publication, especially pp. 380-383).

Fahnestock et al. does not teach a mutant Bacillus strain which grows under alkaline conditions and produces any mutant protease of any amino acid sequence and structure, and has no detectable level of any intracellular or extracellular wild-type protease.

Takagi et al. teach a mutant subtilisin E with enhanced protease activity made by site directed mutagenesis and gene encoding said mutant subtilisin E (see Abstract and entire publication).

According to the Appeal Brief on page 8, high alkaline proteases are defined as "proteases produced by alkalophilic Bacillus strains". According to the specification "alkalophilic bacilli are defined as Bacillus strains that grow under alkaline conditions" (see p. 10, lines 23-25).

Thus, in view of MPEP §2111, page 8 of the Appeal Brief and page 10, lines 23-25, of the specification, claim 50 is deemed to be a genus claim which encompasses any mutant alkalophilic Bacillus strain which grows under alkaline conditions and produces any **mutant protease** of any amino acid sequence and structure, and has no detectable level of any **intracellular or extracellular wild-type protease** of any amino acid sequence and structure resulting from any genetic mutation to the mutant alkalophilic Bacillus strain, where the wild-

type protease is encoded by a gene having any nucleotide sequence and structure.

It would have been obvious to one of ordinary skill in the art at the time the invention was made to replace the Staphylococcus aureus apa-1 gene contained in the plasmid taught by Fahnestock et al., where the said plasmid is contained in a protease-deficient Bacillus host strain, with the gene encoding a mutant subtilisin E taught by Takagi et al. for the purpose of producing a mutant subtilisin E with enhanced protease activity. One of ordinary skill in the art at the time the invention was made would have been motivated to do this because Fahnestock et al. teach that advantage that these protease-deficient Bacillus host strains are superior host strains for the production of foreign proteins since the reduced protease levels allows for the accumulation of produced foreign proteins with less degradation. One of ordinary skill in the art at the time the invention was made would have had a reasonable expectation for success because Fahnestock et al. teach the successful higher production and accumulation of staphylococcal protein A in the taught protease-deficient Bacillus host strains. Thus, the invention of claims 50 and 52 was within the ordinary skill in the art to make and use at the time was made, and was as a whole clearly prima facie obvious.

According to the Appeal Brief on page 8, high alkaline proteases are defined as "proteases produced by alkalophilic Bacillus strains". According to the specification "alkalophilic bacilli are defined as Bacillus strains that grow under alkaline conditions" (see p. 10, lines 23-25).

Thus, in view of MPEP §2111, page 8 of the Appeal Brief and page 10, lines 23-25, of the specification, claim 41 is deemed a genus claim that encompasses a genus of methods for making any **mutant protease** of any amino acid sequence and structure by obtaining any non-reverting mutant alkalophilic Bacillus host that is incapable of producing any **intracellular or extracellular wild-type protease** of any amino acid sequence and structure, wherein the said non-reverting mutant alkalophilic Bacillus host comprises a chromosomal deletion of the gene of any nucleotide sequence and structure encoding the any **intracellular or extracellular wild-type protease** and contains any integration cassette comprising any gene of any nucleotide sequence and structure encoding any **mutant protease** of any amino acid sequence and structure; and growing said non-reverting mutant alkalophilic Bacillus host under conditions to express said mutant high alkaline protease.

Regarding the method encompassed by claims 41, 42, and 45-47 , it would have been obvious to one of ordinary skill in the art at the time the invention was made to modify the method taught by Fahnestock et al. where the Staphylococcus aureus apa-1 gene, present in a plasmid contained in the protease-deficient Bacillus strains due to chromosomal deletion of the subtilisin structural gene (apr), is replaced with the gene encoding a mutant subtilisin E with enhanced protease activity taught by Takagi et al., and then the protease-deficient Bacillus strains taught by Fahnestock et al. are used to express and accumulate the mutant subtilisin E. One of

ordinary skill in the art at the time the invention was made would have been motivated to do this because Fahnestock et al. teach that advantage that these protease-deficient Bacillus host strains are superior host strains for the production of foreign proteins since the reduced protease levels allows for the accumulation of produced foreign proteins with less degradation. One of ordinary skill in the art at the time the invention was made would have had a reasonable expectation for success because Fahnestock et al. teach the successful higher production and accumulation of staphylococcal protein A in the taught protease-deficient Bacillus host strains. Thus, the invention of claims 41, 42, and 45-47 was within the ordinary skill in the art to make and use at the time was made, and was as a whole clearly prima facie obvious.

Conclusion

9. No claim is allowed.

10. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Christian L Fronda whose telephone number is (571)272-0929. The examiner can normally be reached Monday-Friday between 9:00AM - 5:00PM. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ponnathapura N Achutamurthy can be reached on (571)272-0928. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

CLF

PONNATHAPU ACHUTAMURTHY
SUPERVISORY PATENT EXAMINER
TECHNOLOGY CENTER 1600